CASE AUTH/2928/1/17 and AUTH/2929/1/17

ANONYMOUS v PFIZER AND NOVARTIS

Pharmacovigilance compliance, promotion of an unlicensed indication and breach of undertaking

An anonymous, non-contactable complainant, who stated that he/she was a pharmacovigilance (PV) consultant referred to Case AUTH/2847/5/16. The complainant stated that this case contained important PV considerations not previously addressed.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 concerned the promotion of Ultibro Breezhaler (indacaterol (long acting beta agonist (LABA))/ glycopyrronium (long acting muscarinic antagonist (LAMA)) and Seebri Breezhaler (glycopyrronium) by Novartis and Pfizer.

Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD).

The complainant stated that in Case AUTH/2847/5/16 Pfizer (although not the marketing authorisation holder for Ultibro Breezhaler) was obliged to collect and record relevant information including off-label use to pass to the marketing authorisation holder, Novartis.

The complainant stated that the current Ultibro Breezhaler campaign was likely to encourage replacement of fixed dose combinations of inhaled corticosteroids (ICS)/LABAs with the aim of modifying or preventing clinically relevant exacerbations. In the event of increased safety reports of clinically relevant exacerbations associated with morbidly and mortality (however likely or unlikely) associated with Ultibro Breezhaler use, this theoretical PV safety signal resulting from a widespread change in prescribing habits/patterns might be missed in terms of being directly linked with Ultibro Breezhaler off-label use. Information on how the current promotional campaign for Ultibro Breezhaler might lead to a widespread change in prescribing habits/patterns was provided.

The complainant stated that Cases AUTH/2840/4/16 and AUTH/2847/5/16 confirmed that Pfizer knew about the alleged off-label nature of promotional activities in April 2016. In the four months that followed the organisation seemed not to have thoroughly considered the PV implications because by September 2016 the extent of off-label promotion was not curbed as expected but actually intensified as evidenced by the headline, 'Exacerbation risk reduction in your hands' used on an electronic advertisement shown on an exhibition stand at the European Respiratory Society (ERS) congress in London 3-7 September 2016. The copy of the advertisement provided by the complainant referred to both Novartis and Pfizer.

Both companies had failed to identify and clarify what constituted off-label use. It would seem that this failure might have existed for a considerable amount of time which was serious when considering PV obligations. It was likely that potentially thousands of interactions between Pfizer personnel (field or office based) and valid reporters regarding the use of Ultibro Breezhaler to reduce exacerbations in COPD patients had taken place.

The complainant alleged that Pfizer and Novartis had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label resulting in numerous off-label use case reports that had not been collated for PV maintenance obligations.

The complainant alleged that the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was likely to be applicable beyond UK borders such that the number of company interactions where relevant off-label information was not flagged across the whole of Europe would be unacceptably high.

The complainant stated that at the British Thoracic Society (BTS) conference, 7-9 December, Pfizer's campaign for Ultibro Breezhaler included the headline, 'Ultibro Breezhaler, an evidence based solution for patients with COPD with or without a history of exacerbations'.

The clinical development programme for Ultibro Breezhaler included studies where recruited patients had a history of exacerbations (Wedzicha *et al* 2016 and Zhong *et al* 2014) and also at least one study where recruited patients did not have a history of exacerbations (Wedzicha *et al* 2013). The first half of the headline referred to Ultibro Breezhaler being a 'solution' and projected the perception that it was a solution for patients with exacerbations. The complainant alleged that had Pfizer thoroughly considered the pharmacovigilance implications first and developed effective corrective and preventative actions (CAPAs) then continuation of off-label promotion was avoidable.

The complainant stated that in order to understand the legitimacy of the FDC-LABA/LAMA class being promoted for exacerbation risk reduction it was important to consult the relevant regulatory framework ie the guideline on clinical investigation of medicines in the treatment of COPD – EMA/ CHMP/700491/2012. The complainant provided detailed comments including that this document primarily covered the maintenance treatment of COPD and not the treatment and management of acute exacerbations and essentially outlined three possible aims of maintenance treatment.

1 Provide symptomatic relief through improvement of airway obstruction
2 Modify or prevent exacerbations
3 Modify the course of the disease or modify disease progression.

Also discussed was the importance of recognising the severity of exacerbations where the document stated that, '... the rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality, and the usually significantly increased health-care requirement costs'.

Assessment of risk in terms of the rate of moderate or severe exacerbations was the main requirement for a treatment licensed to be used to modify or prevent exacerbations and had distinctive study criteria to meet before a licence was granted for use in COPD patients.

Meeting two criteria enabled a treatment to be licensed specifically for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations. The two criteria highlighted were clearly challenging as demonstrated by Ultibro Breezhaler. In 2016 the manufacturer announced that a pivotal study (NCT01946620 – ClinicalTrials.Gov) did not meet the primary endpoint of demonstrating statistically significant superiority in the reduction of annualised rates of moderate or severe COPD exacerbations when compared to mono-component LABA treatment alone. The manufacturer indicated that the primary endpoint result would not allow it to make a regulatory filing for the COPD indication in Europe. Had this study (NCT01946620) been successful then specific wording of the licence indication for COPD would reflect the existence of respective, suitable, supporting data for clinically relevant exacerbations as was the case for other currently licensed FDC-ICS/LABA medicines in COPD.

An obvious dichotomy existed from a regulatory perspective in that Ultibro Breezhaler could not progress towards a licence in COPD after missing the primary endpoint for a study designed in accordance with the two criteria defined and subsequently the manufacturer simply did not promote Ultibro Breezhaler for use in COPD. Whereas, FDC-LABA/LAMAs were granted licences solely for maintenance treatment aimed at symptomatic relief through improvement of airway obstruction; yet without meeting the two defined study criteria, Ultibro Breezhaler was simultaneously being positioned and promoted as a suitable alternative to licensed FDC-ICS/LABAs for exacerbation risk reduction. In effect, regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction were being circumvented by promoting Ultibro Breezhaler for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations.

The complainant alleged that exhibitor activities for Ultibro Breezhaler at the BTS were in breach of the undertaking for Case AUTH/2847/5/16.

The complainant provided an overview of published evidence for Ultibro Breezhaler in terms of alignment with key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012).

Despite the fact that the study (NCT01946620) involving FDC-fluticasone/formoterol ensured that the clinically relevant primary endpoint – moderate or severe exacerbations was measured and the treatment period was 12 months, progression towards attaining a COPD licence was not possible because the study criteria were challenging and the study eventually missed its primary endpoint. In the case of FDC-LABA/LAMA studies none of the eight Ultibro Breezhaler studies met all three criteria stated, these being clinically relevant primary endpoint for exacerbations, duration of study sufficient to assess exacerbations and above minimal clinically important difference >20% and just one of the eight publications related to Ultibro Breezhaler involved a study where the clinically relevant primary endpoint – moderate or severe exacerbations was measured over a 12 month treatment period (Wedzicha *et al* 2013) and only a 12% reduction in clinically relevant exacerbations vs the comparator was shown (ie below the threshold of 20%).

The lack of Ultibro Breezhaler studies meeting key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012), prompted a broader analysis of other FDC-LABA/LAMAs publications none of the 7 citations involving other FDC-LABA/LAMAs (Buhl *et al* 2015, Celli *et al* 2014, Decramer *et al* 2014, Donohue *et al* 2013, Donohue *et al* 2014, D'Urzo *et al* 2013 and Singh *et al* 2013) met all three criteria.

Out of nine FDC-LABA/LAMAs publications that had a secondary endpoint measure of exacerbations almost all publications did not define exacerbations such that it was not clear to the reader that clinically relevant exacerbations were not measured in these studies. Potentially, this might lead to a misunderstanding and exaggeration of clinical benefit.

The complainant stated that the literature review and assessment undertaken confirmed that there was insufficient evidence to support the use of Ultibro Breezhaler for exacerbation risk reduction. To date, Pfizer and Novartis had simply not undertaken clinical trials in accordance with recommendations in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). This was concerning given the continuation of off-label promotion. Pfizer used the recent FLAME study (Wedzicha *et al* 2016) as the main reference to support the claims appearing in the promotional materials cited by the complainant. It was not entirely clear to the complainant why Novartis, chose not to undertake this study in accordance with recommendations in the guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/700491/2012). It made it problematic

to adequately assess the results alongside other supporting studies for other medicines that were actually licensed to be used in COPD patients with the aim of modifying or preventing clinically relevant exacerbations (EMA/CHMP/700491/2012).

The complainant stated that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient.

The complainant stated that exhibitor activities for Ultibro Breezhaler at the BTS conference 7/9 December suggested that those on the exhibition stand were specifically briefed to discuss the medicine in the context of newly issued recommendations within the GOLD 2017 Report.

The updated GOLD Report represented a positive step forward in simplifying the ABCD matrix which previously posed challenges in categorising COPD patients with three different sub-categories possible depending on the presence of either one or both risk factors, namely, FEV1, staging and exacerbations risk. The updated GOLD Report was however concerning from a patient safety perspective as it stated:

- **'Recommendations by the GOLD Committee for use of any medication are based on the best evidence available from published literature and not on labelling directives from government regulators'.**

    - **FDC-LABA/LAMAs were recommended first-line in category D COPD patients and as step up from a LAMA in category C COPD patients. Both of these two recommendations essentially involved use of FDC- LABA/LAMAs in an unlicensed indication or manner.**

- **'It should be noted that there is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D'.**

    - **FDC-LABA/LAMAs were recommended first-line in category D COPD patients, but there was no evidence that FDC-LABA/LAMAs compared to LAMAs could significantly reduce the risk of clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations.**
    - **Furthermore, although the FLAME study reported that in a secondary endpoint, Ultibro Breezhaler was superior to FDC-fluticasone/ formoterol in terms of clinically relevant moderate or severe exacerbations, this effect was not demonstrated in patients with a history of more than one exacerbation, and category C COPD patients were not included in this study (Wedzicha *et al* 2016).**

The complainant noted that in the GOLD Report there was no ratified European Pharmacovigilance Risk Assessment Committee (PRAC) recommendation stating a positive risk-benefit balance for FDC-ICS/LABAs in COPD (eg the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slight increased risk in terms of pneumonia (Corradi *et al* 2016)). Yet a major factor cited within the updated GOLD Report for recommending usage of FDC-LABA/ LAMAs in an unlicensed indication or manner was the frequently repeated reference to the risk of pneumonia with use of FDC-ICS/LABAs. This seemed not to be balanced because the respective PRAC recommendations were excluded. Moreover, these risks of pneumonia were not qualified in the updated GOLD Report, in terms of not translating into a greater risk of mortality (Festic *et al* 2016).

The complainant alleged that when taking into consideration both Pfizer's continued off-label promotion with the revised GOLD Report recommendations that essentially involved recommending use of FDC-LABA/LAMAs in an unlicensed indication or manner, it was clear that there was a underlying move towards circumventing the regulatory requirements outlined in EMA/ CHMP/700491/2012 related to exacerbation risk reduction by promoting/recommending products for exacerbation risk reduction without these medicines being granted licences that reflected the existence of respective, suitable, support data for clinically relevant exacerbations.

The complainant alleged that the regulatory processes in place to protect public health were being marginalised. If the pharmaceutical industry embarked on charting a strategic direction that inadvertently (or otherwise) undermined the very regulatory foundations that were meant to keep patients safe then the industry was entering unwelcomed territory which inevitably would discredit it.

The obvious concern was whilst an unavoidable delay might actually benefit Pfizer commercially. A similar protracted period of time prior to completion of this PV related PMCPA case would not be in the best interest of patient safety. The complainant therefore urged the PMCPA to prioritise completion of this case if possible given the far reaching patient safety implications.

The detailed response from Pfizer and Novartis is given below.

The Panel was extremely concerned that a complaint had been received which included allegations about Novartis' and Pfizer's activities in relation to pharmacovigilance which was vital for patient safety. There were extensive requirements for pharmacovigilance which went beyond the Code. The Panel could only consider allegations in relation to the requirements in the Code.

The Panel noted the complainant's comments about the regulatory requirements outlined in EMA/CHMP/700491/2012 being circumvented by promoting FDC-indacaterol/glycopyrronium for exacerbation risk reduction without being granted a licence that reflected the existence of respective,

suitable, supporting data for clinically relevant exacerbations. The Panel was concerned about activities in relation to the Code. It was not for the Panel to determine whether Novartis' and Pfizer's activities including clinical trials were in line with the regulatory requirements *per se*.

The Code stated that companies must comply with all applicable codes, laws and regulations to which they are subject. The relevant clause had not been raised and the complainant had not provided evidence that the companies had been found in breach of other laws and regulations.

The Panel noted that the complainant had referred to implications across Europe. The Panel could only consider matters which were covered by the UK Code and/or occurred in the UK. The fact that pharmacovigilance reporting in other countries might be lacking was of concern but was not in itself a matter necessarily covered by the ABPI Code.

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's positive impact on exacerbations of COPD compared to other medicines. The Ultibro SPC was last revised on 10 November 2016. The Panel noted the companies' comments in relation to changes to the SPC.

The Panel noted its rulings in the previous cases, Cases AUTH/2840/4/16 and AUTH/2847/5/16. In particular that in some of the materials at issue in those cases, for example the claim that 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' and 'vs salmeterol/ fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard, no breaches of the Code had been ruled.

Other material was ruled in breach as it did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms. For example boxed text in a leavepiece 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' would not be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. The leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. Breaches of the Code had been ruled including that high standards had not been maintained. Similarly a speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler might give the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading. Breaches of the Code were ruled including that high standards had not been maintained.

The Panel noted that the complaint in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was received in April 2016 and the requisite undertaking was received on 16 September. The ERS congress referred to by the complainant in Cases AUTH/2928/1/17 and AUTH/2929/1/17 took place from 3 – 7 September. This meant that the activities at that meeting were not covered by the requisite undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16. There could be no breach of that undertaking so the Panel ruled no breaches of the Code including Clause 2.

The Panel accepted the companies' submission that the material used at the ERS meeting reiterated topics that had already been considered by the PMCPA and ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel decided that these materials were covered by that ruling and thus decided not to make a separate ruling of breaches of the Code in that regard.

The Panel was concerned that given its rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16 it appeared that the companies had failed in some representative briefing materials to make Ultibro Breezhaler's licensed indication clear. It did not consider that this necessarily meant that the companies had failed to make it clear to staff what constituted off label use of the product as alleged in Cases AUTH/2928/1/17 and AUTH/2929/1/17. Although it was likely that staff might not be clear, the Panel did not consider that the complainant had shown on the balance of probabilities that the companies had failed to adequately train personnel to recognise that the use of FDC-indacaterol/ glycopyrronium to reduce exacerbations in COPD was off label. Further there was no evidence that there would be numerous off label use case reports and if so that these had not been collated for pharmacovigilance maintenance obligations. The Panel therefore ruled no breaches of the Code including Clause 2.

The Panel noted the companies' submission that they were fully committed to protecting and enhancing patient safety and operated extensive, robust scientific services and pharmacovigilance systems. The Panel did not consider that the companies' failures in Cases AUTH/2840/4/16 and AUTH/2847/5/16 necessarily meant that the relevant staff were not fully conversant with pharmacovigilance requirements relevant to their work nor had the complainant provided evidence in that regard. The Panel therefore ruled no breach of the Code.

With regard to the materials used at the BTS Winter meeting in December 2016, the Panel noted the companies' submission that the material provided by

the complainant had not been used at that meeting, it was likely to be a journal advertisement from early 2016 and it preceded the date the undertakings were provided in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel noted, however, that the title of the piece 'Ultibro Breezhaler. An evidence-based solution for patients with or without a history of exacerbations' was the same as the current material provided by Pfizer and Novartis.

The Panel considered that the complainant had not shown, on the balance of probabilities, that the companies had used the Ultibro advertisement he/she provided at the British Thoracic Society (BTS) meeting in December 2016 and had therefore promoted Ultibro Breezhaler for an unlicensed indication at that meeting as alleged. The Panel therefore ruled no breaches of the Code. The Panel also considered that in these circumstances there could be no breach of the undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and thus ruled no breaches in that regard including Clause 2.

With regard to the allegation that there was a suggestion that staff on the stand were specifically briefed to discuss Ultibro in the context of the GOLD 2017 Report, the Panel examined the materials available on the stand. These included Wedzicha *et al* 2016 (FLAME) and various promotional material some of which referred to the GOLD Guidelines including that 'the goal of treatment was to manage symptoms and reduce the risk of exacerbations'.

The Panel noted that Pfizer and Novartis had briefed staff on 18 November 2016 regarding the GOLD 2017 Report. The Panel noted that the companies briefed its staff regarding an important update on materials following the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 on 16 September 2016. The briefing stated 'You must ensure that when you are talking about exacerbation data for, *inter alia*, Ultibro Breezhaler your customers are clear that the reason to prescribe Ultibro Breezhaler is as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It is acceptable to present data about exacerbations as long as the customer is not left with the impression that Ultibro is for treating exacerbations or that the primary reason to prescribe is to reduce exacerbations.

The Panel queried why this had not been re-iterated to staff at BTS considering Ultibro was to be promoted and the briefing regarding the GOLD 2017 Report which had been issued recently. The briefing summarised key points and listed the main considerations with regard to Ultibro Breezhaler. This included that key definitions for patient classifications would be based only on symptoms and exacerbations and that dual bronchodilators such as Ultibro Breezhaler were recommended as first line treatment regardless of their exacerbation risk and prior to the use of ICS marking a significant shift away from ICS containing combination therapies. The instructions also stated that the FLAME study was included as providing evidence for the use of dual bronchodilation; stating that a LAMA/LABA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients. It was important that Pfizer confidently communicated to clinicians the reference behind this statement in order to position Ultibro Breezhaler as the new standard of care for patients with COPD with or without a history of exacerbations.

The briefing material concluded by stating that as could be seen from the significant changes to the GOLD Guidelines which directly impacted Ultibro, treatment decisions were now much more focused on the symptom burden for the patient and LAMA/LABAs had been given a far more prominent role in the management of COPD. This represented a valuable opportunity for the company to provide prescribers with a simple algorithm to follow which would ensure that patients received the right therapy to manage their COPD and increase their chances of living a healthy, active life.

The briefing material referred to Ultibro as 'the evidence based choice of LAMA/LABA for breathless patients regardless of their exacerbation history' and as 'the new standard of care'. In addition, the Panel queried whether the briefing material was sufficiently clear about the need to ensure that any discussion about the reduction in exacerbations should be a benefit of maintenance therapy and not a reason to prescribe *per se*. The Panel considered, on balance, that the briefing material was not sufficiently clear in this regard and thus ruled a breach of the Code.

The Panel did not consider, however, that the complainant had proved, on the balance of probabilities, that based on the exhibitor activities for Ultibro Breezhaler at BTS in December that those on the exhibition stand were specifically briefed to discuss the medicine within the context of the newly issued recommendations within the revised GOLD Report as alleged. The Panel ruled no breach in that regard.

A slide deck for payors (ref UK/ULTSBR/16-0068(1) 'Supporting the management of COPD' consisted of 68 slides including the burden of COPD on the health system, disease management, the benefits of Ultibro Breezhaler and the future of COPD care. The deck referred to the GOLD guidelines that ICS + LABA was recommended for use only in patients in groups C and D (slide 25). This document included claims that Ultibro Breezhaler was an appropriate steroid free option for the patient for whom LABA/ICS was considered (eg slide 31) which also included the Ultibro indication making it clear the primary reason for prescribing Ultibro and therefore no breach was ruled. The FLAME study (Wedzicha *et al* 2016) results were given on slide 32 including a comparison of exacerbation rates of Ultibro and Seretide as well as FEV1 and rescue medication use. The Panel considered the FLAME study results were set within the context of the licensed indication and thus it ruled no breach of the Code.

Material (ref UK/ULTSBR/16-0286) described as 'FLAME Business Card – eprint URL link' promoting

the results of FLAME (Wedzicha *et al* 2016) referred to the exacerbation outcomes and their impact on patients at risk of future exacerbations without setting these in the context of the Ultibro licensed indication. A breach was ruled. In addition, this material implied that the exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. Breaches of the Code were ruled including that high standards had not been maintained. Pfizer and Novartis had failed to comply with their undertakings given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and a breach of the Code was ruled. The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code.

The Panel noted that four webinars were conducted in which health professionals were invited to attend a global broadcast about the updated GOLD Report. Representatives were required to show an introductory slide with all obligatory information including Ultibro's licensed indication for an audience of UK health professionals. The Panel noted its comments above regarding the GOLD briefing and the webinars and considered that whilst the GOLD briefing was not sufficiently clear, the 'upfront' slide required to be shown to UK health professionals set out the indication and therefore the webinars were clear about Ultibro Breezhaler's licensed indication and in that regard were not in breach of the Code.

An anonymous, non-contactable complainant, who stated that he/she was a pharmacovigilance (PV) consultant who regularly looked at published cases to identify PV related cases, referred to Case AUTH/2847/5/16. The complainant stated that this case contained important PV considerations not previously identified and addressed. The complainant referred to Good Pharmacovigilance Practices (GVP) which led to a genuine collaborative and cross-functional approach to product promotion and the importance of a strong culture of PV compliance across an organisation.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 concerned the promotion of Ultibro Breezhaler (indacaterol (long acting beta agonist (LABA))/ glycopyrronium (long acting muscarinic antagonist (LAMA)) and Seebri Breezhaler (glycopyrronium) by Novartis Pharmaceuticals UK Ltd and Pfizer Limited. Ultibro Breezhaler and Seebri Breezhaler were both indicated as maintenance bronchodilator treatments to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). Both products were required to show an inverted black triangle to denote that additional monitoring was required in relation to adverse reactions.

COMPLAINT

The complainant stated that the marketing authorisation holder (MAH) was responsible for continuously monitoring the safety of its medicines, for informing the authorities of any changes that might have an impact on the marketing authorisation, and for ensuring that the product information was kept up-to-date.

Beyond collation of spontaneous safety reports involving adverse events, Article 23 of Directive 2001/83/EC required the MAH to report to the competent authorities any other new information which might influence the evaluation of the benefit-risk balance of the medicine concerned, including data on the use of a medicine outside the terms of its marketing authorisation. Furthermore, chapter V.B.8.5.4 of GVP Module V outlined the specification of post-marketing safety updates and stated that it should include off-label use information sourced within the European Union (EU). Off-label use was use in an unlicensed indication or manner.

There was a legal requirement to include information regarding off-label use in Periodic Safety Update Reports (PSURs) and Risk Management Plans (RMPs) (regardless of whether there was an associated adverse reaction or not). The MAH should have a procedure in place to collect and record relevant information including off-label use in order to competently:

- Identify patterns of use and new safety signals
- Continuously monitor the benefit-risk balance of medicines
- Produce PSURs/Periodic Benefit-Risk Evaluation Report (PBRER)
- Inform regulators of any changes to the benefit-risk balance.

In Case AUTH/2847/5/16 Pfizer (although not the MAH for Ultibro Breezhaler) was obliged, as the distributor/co-promoter, to ensure that a suitable process was in place to collect and record relevant information including off-label use in order to pass on all relevant information to the MAH, Novartis, within timeframes outlined in the Safety Data Exchange Agreement (SDEA) between Pfizer and Novartis.

Patterns of use important to safety signals

The complainant referred to the 2012 benfluorex scandal in France as a reminder of the potential risks of not effectively collating information on off-label use of any medicine especially where it involved exposure to broad patient populations. Benfluorex was routinely used off-label. Eventually it was found to cause fatal valvular heart disease and resulted in major changes to the French regulatory system. A robust system for collating information on off-label use was therefore an important aspect of safeguarding public health.

In the complainants view lessons from the benfluorex incident were applicable to Ultibro Breezhaler because it was not specifically recommended or licensed for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations;

> (in order to modify or prevent exacerbations – clinically relevant exacerbations which are associated with morbidity and mortality i.e.

moderate or severe exacerbations – EMA/CHMP/700491/2012. The complainant's view was that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient. Nor was such use within the terms of the Marketing Authorisation. The complainant stated the relevance of this was discussed below.)

The complainant stated that the current promotional campaign for Ultibro Breezhaler was likely to encourage replacement of fixed dose combinations of inhaled corticosteroids (ICS)/LABAs with the aim of modifying or preventing clinically relevant exacerbations (relevance of specifying exacerbation severity was discussed below). In the event of increased safety reports of clinically relevant exacerbations associated with morbidly and mortality (however likely or unlikely) associated with Ultibro Breezhaler use, this theoretical PV safety signal resulting from a widespread change in prescribing habits/patterns might be missed in terms of being directly linked with Ultibro Breezhaler off-label use. Information on how the current promotional campaign for Ultibro Breezhaler might lead to a widespread change in prescribing habits/patterns was discussed below.

Failure to clarify what constituted off-label use

The complainant stated that Clause 25.1 outlined the requirement to collate information through a scientific service and Clause 15.6 also referred to this obligation from a representative's perspective. Guidance on company procedures relating to the Code section 18 Training; stated that 'all personnel (and other retained by way of contract) must be fully conversant with pharmacovigilance requirements relevant to their work and this must be documented'.

Cases AUTH/2840/4/16 and AUTH/2847/5/16 confirmed that Pfizer knew about the alleged off-label nature of promotional activities in April 2016. In the four months that followed the organisation seemed not to have thoroughly considered the PV implications because by September 2016 the extent of off-label promotion was not curbed as expected but actually intensified as evidenced by the headline, 'Exacerbation risk reduction in your hands' used on an electronic advertisement shown on an exhibition stand at the European Respiratory Society (ERS) congress in London 3-7 September 2016. The copy of the advertisement provided by the complainant referred to both Novartis and Pfizer.

The complainant alleged that neither Pfizer nor Novartis had recognised the off-label use of Ultibro Breezhaler for exacerbation risk reduction given the intensification in the tone of off-label promotion at the ERS congress 2016. Both companies had failed to identify and clarify what constituted off-label use. It would seem that this failure might have existed for a considerable amount of time which was serious when considering ongoing PV maintenance obligations. It was likely that potentially thousands of interactions between Pfizer personnel (field or office based) and valid reporters regarding the use of Ultibro Breezhaler to reduce exacerbations in COPD patients had taken place.

The complainant alleged that Pfizer and Novartis had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label resulting in numerous off-label use case reports that had not been collated for PV maintenance obligations. This training was an essential part of the process that ensured reports of off-label use of medicines associated with an adverse reaction were flagged. In the absence of such specific training the process to flag reports of off-label use was inadequate due to the failure of both Pfizer and Novartis to identify and clarify what constituted off-label use. Failure to clarify what constituted off-label use had been cited as a finding in previous pharmacovigilance inspections by the Medicines and Healthcare products Regulatory Agency (MHRA).

The complainant alleged that the PMCPA ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was likely to be applicable beyond UK borders such that the number of company interactions where relevant off-label information was not flagged across the whole of Europe would be unacceptably high.

Alleged Pharmacovigilance system deficiencies and corrective actions

The complainant stated that these alleged PV system deficiencies would ordinarily expect robust and swift MAH action internally, deriving Corrective And Preventative Actions (CAPAs) including:

1 Referral of findings to the organisation's highest internal safety committee
2 Updating the RMP for the product to capture findings
3 Implementation of corrective and preventative actions related to each finding ie:

   a) Issuing a 'Dear Dr Letter' to rectify the confusion and misunderstanding resulting from prolonged promotional activities that were prohibited
   b) Updating the safety data exchange agreement (SDEA) between Novartis and Pfizer to reflect CAPAs and also to tighten up on off-label reporting processes in general
   c) Re-training all personnel with the aim of identifying and clarifying what constituted off-label use
   d) Amendment of promotional materials and associated briefing documents to comply with signed PMCPA undertakings.

These measures were fundamental to GVP and in the interest of patient safety. It was not possible to assess whether measures 1, 2, 3, 3a, 3b and 3c above had been followed through. Point 3d could be assessed in part through recent scientific journal advertisements and exhibitor activities.

The complainant stated that at a national scientific respiratory conference, 7-9 December, Pfizer's campaign for Ultibro Breezhaler included the

headline, 'Ultibro Breezhaler, an evidence based solution for patients with COPD with or without a history of exacerbations'. A picture of the material was provided.

The clinical development programme for Ultibro Breezhaler included studies where recruited patients had a history of exacerbations (Wedzicha *et al* 2016 and Zhong *et al* 2014) and also at least one study where recruited patients did not have a history of exacerbations (Wedzicha *et al* 2013). The first half of the headline referred to Ultibro Breezhaler being a 'solution' and projected the perception that it was a solution for patients with exacerbations. The complainant alleged that had Pfizer thoroughly considered the pharmacovigilance implications first and developed effective CAPAs then continuation of off-label promotion was avoidable.

Lack of consistency with regulatory framework

The complainant stated that as a PV consultant he/she routinely cross referenced with the latest PV guidance/legislation. Taking a similar approach in order to understand the legitimacy of the FDC-LABA/LAMA class being promoted for exacerbation risk reduction it was important to consult the relevant regulatory framework ie the guideline on clinical investigation of medicines in the treatment of COPD – EMA/CHMP/700491/2012 which replaced the previous guideline Points to Consider CPMP/EWP/562/98, 19 May 1999.

This document primarily covered the maintenance treatment of COPD and not the treatment and management of acute exacerbations and essentially outlined three possible aims of maintenance treatment.

1 Provide symptomatic relief through improvement of airway obstruction
2 Modify or prevent exacerbations
3 Modify the course of the disease or modify disease progression.

Also discussed was the importance of recognising the severity of exacerbations where the document stated that, '... the rate of moderate or severe exacerbations is a clinically relevant endpoint related to the associated morbidity and mortality, and the usually significantly increased health-care requirement costs'.

Assessment of risk in terms of the rate of moderate or severe exacerbations was the main requirement for a treatment licensed to be used to modify or prevent exacerbations and had distinctive study criteria to meet before a licence was granted for use in COPD patients as outlined in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). These being:

1 A requirement to undertake one or more comparative studies over 12 months or more that measured the reduction in moderate (clinical interventions with oral steroids +/- antibiotics) or severe (hospitalisation) exacerbations, as a primary-endpoint.
2 Reduction in frequency of 20% (minimally important clinical difference) had been suggested as being clinically relevant vs the comparator in the reduction of moderate or severe exacerbations. This was also acknowledged by the National Institute for Health and Care Excellence (NICE) in its evidence summary review of Ultibro Breezhaler.

Meeting these two criteria enabled a treatment to be licensed specifically for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations (in order to modify or prevent exacerbations – clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations - EMA/CHMP/700491/2012). The two criteria highlighted above, were clearly challenging as demonstrated by Ultibro Breezhaler. In the summer of 2016 the manufacturer announced that a pivotal study (NCT01946620 – ClinicalTrials.Gov) undertaken in accordance with the criteria mentioned did not meet the primary endpoint of demonstrating statistically significant superiority in the reduction of annualised rates of moderate or severe COPD exacerbations when compared to mono-component LABA treatment alone. The manufacturer indicated that the primary endpoint result would not allow it to make a regulatory filing for the COPD indication in Europe. The chief executive officer stated that, '... COPD is a complex and highly variable disease and these trial results highlight the challenge in demonstrating reductions of exacerbations ...'. Had this study (NCT01946620) been successful then specific wording of the licence indication subsequently granted for COPD would reflect the existence of respective, suitable, supporting data for clinically relevant exacerbations as was the case for other currently licensed FDC-ICS/LABA medicines in COPD.

An obvious dichotomy existed from a regulatory perspective in that Ultibro Breezhaler could not progress towards a licence in COPD after missing the primary endpoint for a study designed in accordance with the two criteria defined above and subsequently the manufacturer simply did not promote Ultibro Breezhaler for use in COPD. Whereas, FDC-LABA/LAMAs were granted licences solely for maintenance treatment aimed at symptomatic relief through improvement of airway obstruction; yet without meeting the two defined study criteria, Ultibro Breezhaler was simultaneously being positioned and promoted as a suitable alternative to licensed FDC-ICS/LABAs for exacerbation risk reduction. In effect, regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction were being circumvented by promoting Ultibro Breezhaler for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations.

The complainant alleged that exhibitor activities for Ultibro Breezhaler at the national scientific respiratory conference, 7-9 December, were in breach of the undertaking associated with Case AUTH/2847/5/16 when taking into consideration the regulatory framework described above.

Insufficient evidence for exacerbation risk reduction with Ultibro Breezhaler based on criteria defined in EMA/CHMP/700491/2012

The complainant provided a table which was an overview of published evidence for Ultibro Breezhaler in terms of alignment with key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012):

- Clinically relevant primary endpoint – Moderate (clinician intervention with oral steroids +/- antibiotics) or severe (hospitalisation) exacerbations
- Treatment period of 12 months or more
- Reduction of frequency of 20% in the rate of moderate or severe exacerbations versus comparator.

Eight publications for Ultibro Breezhaler were identified and evaluated (Bateman *et al* 2013, Dahl *et al* 2013, Gebner *et al* 2014, Mahler *et al* 2014, Vogelmeier *et al* 2013, Wedzicha *et al* 2013, Wedzicha *et al* 2016 and Zhong *et al*).

Despite the fact that the study (NCT01946620) involving FDC-fluticasone/formoterol ensured that the clinically relevant primary endpoint – moderate or severe exacerbations was measured and the treatment period was 12 months, progression towards attaining a COPD licence was not possible because the study criteria were challenging and the study eventually missed its primary endpoint. In the case of FDC-LABA/LAMA studies:

- None of the eight Ultibro Breezhaler studies met all three criteria stated above
- Just one of the eight publications related to Ultibro Breezhaler involved a study where the clinically relevant primary endpoint – moderate or severe exacerbations was measured over a 12 month treatment period (Wedzicha *et al* 2013) and only a 12% reduction in clinically relevant exacerbations vs the comparator was shown (ie below the threshold of 20%).

The lack of Ultibro Breezhaler studies meeting key study criteria for exacerbation risk reduction stated in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012), prompted a broader analysis of other FDC-LABA/LAMAs publications:

- None of the 7 citations involving other FDC-LABA/LAMAs (Buhl *et al* 2015, Celli *et al* 2014, Decramer *et al* 2014, Donohue *et al* 2013, Donohue *et al* 2014, D'Urzo *et al* 2013 and Singh *et al* 2013) met all three criteria.

Out of nine FDC-LABA/LAMAs publications that had a secondary endpoint measure of exacerbations almost all publications did not define exacerbations such that it was not clear to the reader that clinically relevant exacerbations were not measured in these studies. Potentially, this might lead to a misunderstanding and exaggeration of clinical benefit.

The complainant stated that the literature review and assessment undertaken confirmed that there was insufficient evidence to support the use of Ultibro Breezhaler for exacerbation risk reduction. To date, Pfizer and Novartis had simply not undertaken clinical trials in accordance with recommendations in the guideline on clinical investigation of medicines in the treatment of COPD (EMA/CHMP/700491/2012). This was concerning given the continuation of off-label promotion.

Pfizer used the recent FLAME study (Wedzicha *et al* 2016) as the main reference to support the claims appearing in the promotional materials cited by the complainant. It was not entirely clear to the complainant why the sponsor of the study, Novartis, chose not to undertake this study in accordance with recommendations in the guideline on clinical investigation of medicinal products in the treatment of COPD (EMA/CHMP/700491/2012). It made it problematic to adequately assess the results alongside other supporting studies for other classes of medicines that were actually licensed to be used in COPD patients with the aim of modifying or preventing clinically relevant exacerbations (EMA/CHMP/700491/2012). Therefore regulators would need reassurance via further data and studies which might also clarify understanding in specific areas such as:

- The primary outcome was 'all exacerbations' where 40% were essentially a brief worsening of breathlessness (ie mild exacerbations). Ultimately these were not clinically relevant exacerbations which were associated with morbidity and mortality and thus unlikely to impact healthcare and disease progression to the same extent as clinically relevant exacerbations. A further study was required with the primary endpoint moderate to severe exacerbations.
- Data on previous treatment history of the study population seemed to suggest that a significant proportion of patients were already on dual LABA/LAMA therapy albeit via separate inhalers. It was important to understand if this could impact the two study treatment arms disproportionally as all patients were stepped-down to tiotropium (LAMA) during the run-in phase and then subsequently stepped-up during the treatment phase to an Ultibro Breezhaler or FDC-fluticasone/salmeterol.
- The study population categorised in terms of airflow limitation mainly included Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2 (33.3%) and GOLD stage 3 (58%) patients. It was important to understand if this could impact results. Also, only approximately half had inhaled corticosteroids prior to study entry which supported the deduction that a significant proportion of patients were likely to be already on dual LABA/LAMA therapy prior to study entry.
- Recent studies involving COPD drug classes had observed a background rate of clinically relevant exacerbations of less than 1 event/patient/year rate (Dransfield *et al* 2013, Wedzicha *et al* 2014, Albert *et al* 2011 and Martinez *et al* 2015). So the actual clinically relevant exacerbation rate of around 1 vs.0.9 predicted leading to a surprisingly

greater magnitude in risk reduction compared to 'all exacerbations' contrasted with study protocol assumptions. In comparison to other recent studies, those four studies above and Wedzicha *et al* 2016, this anomaly also needed to be better understood in relation to geographic location of study centres.
- Almost 10% were excluded in the per protocol analysis for the primary end-point only and per protocol analysis was not available in the publication for secondary endpoint results making their evaluation challenging.

The complainant stated that the totality of data suggested that the extent of protection from bronchodilation via dual bronchodilators, against the development of clinically relevant exacerbations was insufficient.

Marginalising the regulatory framework

The complainant stated that exhibitor activities for Ultibro Breezhaler at the national scientific respiratory conference 7/9 December suggested that those on the exhibition stand were specifically briefed to discuss the medicine in the context of newly issued recommendations within the GOLD 2017 Report.

The recently revised GOLD Report was an important reference and was compiled by international experts. The update represented a positive step forward in simplifying the ABCD matrix which previously posed challenges in categorising COPD patients with three different sub-categories possible depending on the presence of either one or both risk factors, namely, FEV1, staging and exacerbations risk. The recent update of the GOLD Report was however concerning from a patient safety perspective as it stated:

- 'Recommendations by the GOLD Committee for use of any medication are based on the best evidence available from published literature and not on labelling directives from government regulators'.
    - FDC-LABA/LAMAs were recommended first-line in category D COPD patients and as step up from a LAMA in category C COPD patients. Both of these two recommendations essentially involved use of FDC-LABA/LAMAs in an unlicensed indication or manner.
- 'It should be noted that there is a lack of direct evidence supporting the therapeutic recommendations for patients in groups C and D'.
    - FDC-LABA/LAMAs were recommended first-line in category D COPD patients, but there was no evidence that FDC-LABA/LAMAs compared to LAMAs could significantly reduce the risk of clinically relevant exacerbations which were associated with morbidity and mortality ie moderate or severe exacerbations.
    - Furthermore, although the FLAME study reported that in a secondary endpoint, Ultibro Breezhaler was superior to FDC-fluticasone/formoterol in terms of clinically relevant moderate or severe exacerbations, this effect was not demonstrated in patients with a history of more than one exacerbation, and category C COPD patients were not included in this study (Wedzicha *et al* 2016).

The complainant noted that in the GOLD Report there was no ratified European Pharmacovigilance Risk Assessment Committee (PRAC) recommendation stating a positive risk-benefit balance for FDC-ICS/LABAs in COPD (eg the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slight increased risk in terms of pneumonia (Corradi *et al* 2016)). Yet a major factor cited within the updated GOLD Report for recommending usage of FDC-LABA/LAMAs in an unlicensed indication or manner was the frequently repeated reference to the risk of pneumonia with use of FDC-ICS/LABAs. This seemed not to be balanced because the respective PRAC recommendations were excluded. Moreover, these risks of pneumonia were not qualified in the updated GOLD Report, in terms of not translating into a greater risk of mortality (Festic *et al* 2016).

The complainant alleged that when taking into consideration both Pfizer's continued off-label promotion with the revised GOLD Report recommendations that essentially involved recommending use of FDC-LABA/LAMAs in an unlicensed indication or manner, it was clear that there was a underlying move towards circumventing the regulatory requirements outlined in EMA/CHMP/700491/2012 related to exacerbation risk reduction by promoting/recommending products for exacerbation risk reduction without these medicines being granted licences that reflected the existence of respective, suitable, support data for clinically relevant exacerbations.

Prescribing boundaries for the use of medicines defined by their marketing authorisation granted by regulatory agencies were also important in ensuring clarity for related PV obligations.

The complainant alleged that the regulatory processes in place to protect public health were being marginalised through the actions described above. If the pharmaceutical industry embarked on charting a strategic direction that inadvertently (or otherwise) undermined the very regulatory foundations that were meant to keep patients safe then the industry was entering unwelcomed territory which inevitably would discredit it.

Vilhelmsson et al 2016 'Pharmaceutical Industry Off-label Promotion and Self-regulation. A Document Analysis of Off-label Promotion Rulings by the UK PMCPA 2003-2012'.

The complainant stated that the evaluation undertaken by Vilhelmsson *et al* 2016 was an area of research that was of significant relevance to much of what had already been discussed and a major factor in taking the step to submit the complaint.

Within the authors' conclusion was a recommendation to UK authorities to:

'... consider introducing increased incentives and protection for whistleblowers combined with US-style government investigations and meaningful sanctions.'

The complainant stated this was the main reason for remaining anonymous as the complainant.

Pfizer knew about the alleged off-label nature of promotional activities in April 2016. During a prolonged period of over eight months whilst the case remained ongoing, Pfizer continued to press ahead with off-label promotion and actually intensified the tone of off-label promotion during this period. Pfizer never seemed to have taken a step back to reflect and consider the PV implications of its actions. Vilhelmsson *et al*'s suggestion that current sanctions might not go far enough seemed to reflect the case of Pfizer with its continuation of off-label activities and probably anticipated that the eventual sanctions would be 'palatable'. This situation might also reflect weakness in the SDEA between Novartis and Pfizer. If Pfizer was the MAH perhaps it would have taken appropriate action much earlier.

The obvious concern was whilst an unavoidable delay might actually benefit Pfizer commercially in seeing a similar protracted period of time prior to completion of this PV related PMCPA case, it certainly would not be in the best interest of patient safety. If a prolonged period of time were to elapse whereby scores of company interactions where relevant off-label information was not flagged across the whole of Europe continued, this would be unacceptable. The complainant therefore urged the PMCPA to prioritise completion of this case if possible given the far reaching patient safety implications.

When writing to Pfizer and Novartis the Authority asked the companies to respond in relation to Clauses 2, 3.2, 7.2, 9.1, 15.9, 16.2 and 29 in addition to Clauses 25.1 and 15.6 cited by the complainant.

RESPONSE

The response was provided on behalf of both Pfizer Limited and its alliance partner Novartis Pharmaceuticals UK Limited.

Pfizer and Novartis submitted that the topics covered in the complaint were wide-ranging and many fell outside the scope of the Code for example, comments regarding pharmacovigilance systems, the CHMP guideline for clinical investigation of medicines in the treatment of COPD and the recently revised GOLD Global Strategy for the Diagnosis, Management and Prevention of COPD. The companies focused their response on the topics that they considered fell within the scope of the Code. The companies highlighted the following general points which they submitted were important to provide context to the response:

1 Ultibro Breezhaler, a fixed dose combination of two bronchodilators, was indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

2 Much of the complaint was based on the assertion that Ultibro Breezhaler was being promoted and used off-label. The complainant stated that it was not specifically recommended or licensed for use in symptomatic COPD patients despite bronchodilator therapy with a history of exacerbations. The companies absolutely disagreed with this assertion. The licensed indication for Ultibro Breezhaler, as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD, did not stipulate or preclude its use in any subgroup of symptomatic COPD patients including presence or absence of a history of exacerbations, previous therapy, or success of previous therapy. Therefore, as established in Cases AUTH/2840/4/16 and AUTH/2847/5/16, use of Ultibro Breezhaler in adults with COPD who required maintenance bronchodilator therapy to relieve symptoms, irrespective of a history of exacerbations, was entirely within the licensed indication.

3 Following the rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16, Novartis and Pfizer each gave undertakings that in the promotion of Ultibro Breezhaler, reference to reduced exacerbation would be set within the context of the primary reason to prescribe, ie maintenance therapy to relieve symptoms of COPD. However, it should also be noted that claims for a benefit for Ultibro Breezhaler in reducing exacerbations were deemed acceptable within the context of the primary reason to prescribe ie as a maintenance therapy to relieve symptoms. Subsequently, marketing and promotion remained focused on this primary reason to prescribe Ultibro Breezhaler.

4 Elements of the complaint reflect topics considered in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and referred to events which predated the rulings in these cases.

Licensed indication

The companies disagreed with the complainant's assertion that Ultibro Breezhaler was not licensed for use in COPD patients with a history of exacerbations; it might be used as a maintenance bronchodilator in COPD patients with or without exacerbations. Furthermore, Section 5.1 of the Ultibro Breezhaler SPC included data on the various cohorts of patient types and outcomes studied in the clinical development programme (this included patients with a history of exacerbations and the effect of Ultibro Breezhaler on COPD exacerbations). Results from the FLAME study (Wedzicha *et al* 2016), demonstrating the non-inferiority (and superiority) of Ultibro Breezhaler vs fluticasone/salmeterol in rate of all COPD exacerbations, had recently been added to this section of the SPC. The Ultibro Breezhaler SPC did not include any restrictions, contraindications or special warnings or precautions for the use of Ultibro Breezhaler in COPD patients with a history of exacerbations. Consequently, data relating to exacerbation risk reduction, or other clinically relevant endpoints described in Section 5.1, might

be used in promotional materials as long as these were set within the context of the primary reason to prescribe Ultibro Breezhaler (ie as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD), consistent with Clause 3.2 and the rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16.

Additionally, the complainant's reference to benfluorex was irrelevant as this medicine was initially approved for use as a hypolipidemic and hypoglycemic agent in patients with diabetes and was subsequently used off-label in the general population as an anorexic, ie the off-label use was in a different population and with a different clinical objective compared with on-label use. Furthermore, this off-label use continued despite the fact that similar medicines (fenfluramine and dexfenfluramine) had been withdrawn from many markets because they were known to be associated with pulmonary hypertension and valvular insufficiency. In contrast, Ultibro Breezhaler had been extensively studied within the COPD population, including in patients with a history of exacerbations and who had been on previous bronchodilator therapy, and was found to have a favourable benefit:risk profile. The companies were concerned that, if published in the Case report, this inaccurate comparison between benfluorex and Ultibro Breezhaler had the potential to cause unwarranted alarm amongst health professionals and COPD patients which could lead to patients inappropriately stopping treatment and their condition deteriorating.

Collation of information through a scientific service

With regard to the complainant's reference to the obligations of pharmaceutical companies to have a scientific service to compile and collate information relating to the use of their products, including safety information, Novartis and Pfizer pointed out that the complainant did not make any specific complaint or provide any evidence of alleged non-compliance in this respect.

Novartis and Pfizer submitted that they were fully committed to protecting and enhancing patient safety and operated extensive and robust scientific services and pharmacovigilance systems which complied with the relevant regulatory and legal frameworks and with Clause 25.1. All personnel in both companies were trained on requirements to transmit information received relating to use of medicines, including reports of adverse reactions, to the respective scientific service as required by Clause 15.6.

Novartis and Pfizer stated that they collected, processed and reported all safety data according to worldwide regulatory requirements, and provided integrated medical safety evaluations and risk-benefit assessments for all marketed or investigational products. Single and aggregate safety reports were submitted to the worldwide regulatory authorities as required. Dedicated safety teams performed continuous monitoring of the product-risk-benefit profile and supported the pharmacovigilance activities from a medical perspective including medical assessment of Individual Case Safety Reports (ICSRs), preparation of aggregated safety reviews including Development Safety Update Reports (DSURs) and Periodic Safety Update Reports (PSURs), evaluation of the product safety profiles with appropriate reflection in Company Core Data Sheets (CDS), identification of new or changing safety signals including impact and their medical management and identification of risks, preparation of Risk Management Plans (RMPs) and relevant global risk management systems including risk minimization activities.

All Novartis and Pfizer employees completed adverse event (AE) training on an annual basis and were fully aware of their obligations for safety reporting. Where a third party managed activities on behalf of Novartis or Pfizer, it would ensure that the AE training was completed. Novartis and Pfizer each maintained a standard operating procedure (SOP) addressing requirements for AE training (Novartis SOP-7018026 and Pfizer Corporate Policy CP903, respectively).

Exhibition stand at European Respiratory Society (ERS) meeting

The complainant's comments regarding an exhibition stand at the ERS meeting appeared to reiterate topics which had already been ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. Consequently the companies had not provided any materials relating to this meeting but would be happy to do so if requested.

Novartis and Pfizer gave undertakings to ensure that, in the promotion of Ultibro Breezhaler, reference to reduced risk of exacerbations would be set within the context of the primary reason to prescribe, ie maintenance therapy to relieve symptoms of COPD. The ERS meeting was held 3-7 September 2016. Novartis and Pfizer received the PMCPA's ruling after the ERS meeting had closed and the undertakings were provided to the PMCPA on 16 September 2016. Since the undertakings had not been given at the time of the ERS meeting, they could not have been breached then and therefore the companies denied a breach of Clause 29.

In accordance with the undertakings, promotional and training materials were revised or withdrawn and sales personnel were briefed regarding the requirements of the PMCPA ruling. As evidence of adherence to its undertakings, the companies provided a list of the materials that were withdrawn following the ruling and the briefing delivered to representatives on the withdrawals (which was shared by email and WebEx meeting). In total, 115 items were withdrawn of which 28 were revised and recertified. Four revised items were provided as examples, these being the most comprehensive and therefore representative of the revisions made. Five of the revised items were sales materials. The revised sales aid, a FLAME clinical summary and a FLAME leavepiece were provided. A further five items were payor materials and the payor slide deck was provided. Fifteen of the revised items were on demand webinars; these were edited to add the licensed indication for Ultibro Breezhaler

at the beginning of each webinar and at relevant sections throughout. Additionally, all speaker slide decks were reviewed and certified to ensure that the licensed indication was clearly presented as the primary reason to prescribe Ultibro Breezhaler.

Training of personnel on pharmacovigilance requirements

The complainant alleged that Novartis and Pfizer had previously failed to adequately train personnel to recognise that the use of Ultibro Breezhaler to reduce exacerbations in COPD was off-label. The ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 addressed this point and concluded that information relating to Ultibro Breezhaler and exacerbation risk reduction, consistent with the particulars listed in the SPC, might be used in promotion provided that exacerbation risk reduction was not promoted as the primary reason to prescribe. Novartis and Pfizer provided undertakings in this respect on 16 September 2016, as described above.

There did not appear to be an allegation of non-compliance in this respect subsequent to the companies' undertakings and no evidence to this effect had been provided. The companies submitted that the briefing provided to representatives following the ruling complied with the Code and the companies' undertakings. Therefore there was no breach of Clause 15.9.

Furthermore, as described above, all personnel in both companies were trained on pharmacovigilance requirements relevant to their work as detailed in Novartis SOP-7018026 and Pfizer Corporate Policy CP903, respectively. Therefore there was no breach of Clause 16.2.

British Thoracic Society (BTS) Winter Meeting

The BTS Winter Meeting was held 7-9 December 2016 and the companies assumed this was the 'national scientific respiratory conference' referred to by the complainant. Materials on display at the Pfizer exhibition stand had been newly created and had been reviewed and certified as reflecting the ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16.

The item referred to by the complaint, with the headline 'Ultibro Breezhaler. An evidence-based solution for patients with COPD with or without a history of exacerbations' was not an item used at the BTS; due to the poor quality of the image and the fact that the job bag number was not shown in the image the companies were not able to accurately determine the instance of use the cited material had been extracted from, but it was likely to be a journal advertisement from early 2016 (and certainly preceded the undertakings given by Novartis and Pfizer of 16 September 2016). If deemed necessary, if a clearer image of the item or its job bag number was provided the companies could then source the item and provide a copy.

Novartis and Pfizer submitted that they always aimed to fully comply with the Code and were confident that all activities and materials which supported Ultibro Breezhaler were firstly in accordance with its marketing authorisation and secondly not inconsistent with the particulars listed in the SPC. Furthermore, the undertakings had been complied with. Therefore the companies concluded that there had been no breach of Clauses 3.2 or 29 of the Code. Information, claims and comparisons made in these materials and activities were accurate, balanced, fair, objective and unambiguous and were not misleading. The companies therefore concluded that there had been no breach of Clause 7.2.

The companies provided copies of all materials displayed or available at the BTS stand and briefings for staff manning the stand; these included a general 'stand crew' briefing and a briefing on the results of the CRYSTAL study which were being presented at the BTS meeting.

Out of scope topics

The companies submitted that the complainant's comments on EU directives and guidelines, including those referring to PSURs, RMPs, and clinical investigation of medicines were outside the scope of the Code and consequently not addressed. The companies noted that there were a number of factual inaccuracies contained in the complainant's comments on these topics, in particular the remarks about the clinical investigation of medicines. The companies requested the opportunity to address these inaccuracies in further detail should these areas form part of the PMCPA's substantive review.

The companies stated that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was an independent body of clinical experts which developed evidence-based strategy documents for COPD management and worked with health professionals and public health officials to raise awareness of COPD and to improve prevention and treatment of this lung disease for patients around the world. The complainant's comments on GOLD's recently revised guidelines on the management of COPD fell outside the scope of the Code and consequently the companies did not address these.

Summary

The companies submitted that high standards had been maintained and there had been no instances of bringing discredit upon the pharmaceutical industry and there had therefore no breach of Clauses 9.1 or 2.

Further Information

Following a request for further information, Pfizer and Novartis submitted a joint response and clarified their comment about the revised GOLD 2017 Report. The companies noted that the complainant was critical of the GOLD 2017 Report; in their view the derivation of the GOLD recommendations and what the GOLD panel of experts deemed appropriate management strategies for COPD patients, including the evidence it chose to review or not, fell out of scope of the Code. The GOLD committee was an independent body of clinical experts which developed evidence-based strategy documents for COPD management. The manner in which it operated was not governed by the Code.

The companies agreed, however, that any of their materials that related to the GOLD 2017 Guidelines might fall under the remit of the Code.

Pfizer and Novartis answered the questions raised by the Panel.

Representatives briefing about the GOLD 2017 Guidelines:

The companies stated that all representatives, including those on the exhibition stand at the BTS meeting, received instruction about the updated GOLD 2017 Guidelines. A copy of the representative briefing issued on 18 November 2016 was provided.

Pfizer and Novartis explained that four spotlight webinars were conducted in which health professionals were invited to attend a global broadcast about the new GOLD 2017 Guidelines. These webinars were organised by Novartis Pharma AG, based in Switzerland, for a global audience and were certified in accordance with the Code through the Novartis-Pfizer Alliance Zinc platform. The webinars ran on 30 November 2016 (twice) and 1 December 2016 (twice) and featured live talks from two international key opinion leaders, both of whom were authors of the GOLD 2017 Guidelines, after an introduction from a Novartis global medical director. All representatives were briefed to organise webinar meetings and they were given a flyer to invite health professionals to the webinars. Representatives were sent a second briefing before the webinars instructing them to show an introductory slide with all the obligatory information for an audience of UK health professionals, including the licensed indication for Ultibro. The introductory slide was needed as the slide decks shown at the webinar were produced for a global audience. These were certified before the meeting (copies of the briefings, the flyer and of the slides were provided).

At the time of the BTS Congress (7-9 December 2016) there were no Novartis-Pfizer Alliance materials in circulation that referred to the updated GOLD 2017 Guidelines.

The companies noted that whilst the representative briefing material issued in November 2016 referred to 'next steps' including incorporation of the GOLD 2017 Guidelines into materials (representative triggered email, sales aid etc) over the coming months and generation of a simple leavepiece, none of these had yet been finalised.

Representatives Activity at the BTS Congress 7-9 December 2016:

The companies explained that eight representatives worked on the promotional stand at the BTS meeting. They had been briefed about the new GOLD 2017 Guidelines as described above which was provided before the BTS meeting and was not connected with it. This was in addition to the BTS 'stand crew' briefing and a briefing on the results of the CRYSTAL study, which were to be presented at the BTS Congress and referred to previously. Representatives had also been briefed about the undertaking to the PMCPA, also referred to previously. No specific briefing on the GOLD 2017 Guidelines was issued to the representatives attending the BTS Congress.

The GOLD 2017 Guidelines went live on the GOLD website in November 2016 to coincide with World COPD Day.

Pfizer and Novartis explained that there were significant changes to the GOLD 2017 Guidelines compared with the previous edition; treatment decisions became much more focused on the symptom burden for the patient. This emphasis was on symptomatic treatment and a recognition of the clinical evidence of bronchodilation in all patients regardless of exacerbation history. In this regard, the GOLD 2017 Guidelines were in line with the Ultibro licensed indication as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD.

The companies stated that they had used the GOLD Guidelines as follows:

1 Since the publication of the 2017 GOLD Guidelines, all Ultibro materials had been reviewed and reference checked. Where previous GOLD Guidelines were referenced, information provided about the GOLD Guidelines had been reviewed and, where necessary, revised to be consistent with the GOLD 2017 Guidelines. References had been updated accordingly.

2 Four Spotlight Webinars had been conducted in which health professionals were invited to attend a broadcast about the new guidelines. These were described above as activities prior to the BTS meeting.

3 A local account manager sales aid referred to as the Value Slide Deck had been updated and re-issued (replacing UK/ULTSBR/16-0068). The revised material included information about the GOLD 2017 Guidelines.

4 A health professional master speaker deck had been updated which included information about the GOLD 2017 Guidelines.

PANEL RULING

The Panel noted that the complainant was anonymous and although a mailing address had been provided there was no response to a letter sent to that address. Anonymous complaints were accepted and like all complaints judged on the evidence provided by the parties. The complainant had the burden of proving his/her complaint on the balance of probabilities.

The Panel was extremely concerned that a complaint had been received which included allegations about Novartis' and Pfizer's activities in relation to pharmacovigilance which was vital for patient safety. There were extensive requirements for pharmacovigilance which went beyond the Code. The Panel could only consider allegations in relation to the requirements in the Code.

The Panel noted the complainant's allegations about the regulatory requirements outlined in EMA/CHMP/700491/2012 being circumvented by promoting FDC-indacaterol/glycopyrronium for exacerbation risk reduction without being granted a licence that reflected the existence of respective, suitable, supporting data for clinically relevant exacerbations. The Panel was concerned about activities in relation to the Code. It was not for the Panel to determine whether Novartis' and Pfizer's activities including clinical trials were in line with the regulatory requirements *per se*.

Clause 1.11, however, stated that companies must comply with all applicable codes, laws and regulations to which they are subject. This clause had not been raised and the complainant had not provided evidence that the companies had been found in breach of other laws and regulations.

The Panel noted that the complainant had referred to implications across Europe. The Panel could only consider matters which were covered by the UK Code and/or occurred in the UK. The fact that pharmacovigilance reporting in other countries might be lacking was of concern but was not in itself a matter necessarily covered by the ABPI Code.

The Panel noted that both Ultibro Breezhaler and Seebri Breezhaler were indicated as maintenance bronchodilator treatments to relieve symptoms in adult patients with COPD. Section 5.1 of the respective SPCs referred to each medicine's positive impact on exacerbations of COPD compared to other medicines. The Ultibro SPC was last revised on 10 November 2016. The Panel noted the companies' comments in relation to changes to the SPC.

Rulings in Case AUTH/2840/4/16 and AUTH/2847/5/16

The Panel noted its rulings in the previous cases, Cases AUTH/2840/4/16 and AUTH/2847/5/16. In particular that in some of the materials at issue in those cases, for example the claim that 'Ultibro Breezhaler offers benefits beyond current standard COPD maintenance therapies' and 'vs salmeterol/fluticasone Ultibro Breezhaler can significantly reduce your patients' rate of moderate or severe exacerbations' appeared to be a consequence of using Ultibro Breezhaler as a maintenance therapy and not the reason to prescribe *per se*, as alleged. In that regard, no breach of Clause 3.2 was ruled. Given the context in which it appeared, the claim was not misleading with regard to the licensed indication for Ultibro Breezhaler. No breach of Clause 7.2 was ruled. High standards had been maintained. No breach of Clause 9.1 was ruled.

An Ultibro Breezhaler training course presentation (ref UK/ULT/15-0474) referred to COPD maintenance and that health professionals effectively control COPD symptoms through optimal bronchodilation as a cornerstone of COPD management. In a section entitled 'Ultibro Campaign Material "Benefits Beyond"', the structure of the sales aid was discussed and a flow diagram included a box labelled 'Ultibro promise exacerbations'. Three subsequent slides discussed exacerbation data using the same slides as used in the sales aid. The Panel considered that the training presentation could have benefitted from a more explicit statement as to the licensed indication for Ultibro Breezhaler and that any reduction in exacerbations was to be discussed as a benefit of maintenance therapy and not as a reason to prescribe *per se*. Nonetheless, on balance, the Panel did not consider that the material encouraged representatives to promote Ultibro Breezhaler for exacerbation reduction. No breach of Clause 15.9 was ruled. The Panel considered that high standards had been maintained. No breach of Clause 9.1 was ruled.

Other material was ruled in breach of Clauses 3.2 and 7.2 as it did not clearly state that Ultibro Breezhaler was a maintenance therapy to relieve COPD symptoms. For example boxed text in a leavepiece 'Reduces exacerbation risk beyond tiotropium (open label) and [salmeterol/fluticasone]' would not be read within the context of the licensed indication. In the Panel's view the leavepiece implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction in exacerbations being a benefit of using the medicine as maintenance therapy. The leavepiece was inconsistent with the particulars listed in the Ultibro Breezhaler SPC and a breach of Clause 3.2 was ruled. The leavepiece implied that that exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

A speaker slide deck (ref UK/ULT/16-0025) entitled 'Evolving science; Dual bronchodilation' examined the burden of COPD and the challenges of treatment and included an overview of clinical studies for, *inter alia*, Ultibro Breezhaler. In the Panel's view, given the length of the slide deck and the number of topics discussed, it was possible that, after 101 slides, some viewers would have forgotten exactly what Ultibro Breezhaler was indicated for; some viewers might be left with the impression that Ultibro Breezhaler could be prescribed for the reduction of exacerbations *per se* which was not consistent with the particulars listed in its SPC. A breach of Clause 3.2 was ruled. That the presentation implied that Ultibro Breezhaler could be used to reduce COPD exacerbations and was a primary reason to prescribe the product was misleading and a breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such. The Panel noted its rulings and comments in relation to Ultibro and Seebri (not referred to here) but considered that the matters were not such as to bring discredit upon, or reduce confidence in, the industry. No breach of Clause 2 was ruled.

Cases AUTH/2928/1/17 and AUTH/2929/1/17

The Panel noted that the complaint in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was received on 25 April 2016. The companies were notified of the Panel's rulings on 8 September and the requisite undertaking was received on 16 September. The ERS

congress referred to by the complainant in Cases AUTH/2928/1/17 and AUTH/2929/1/17 took place from 3 – 7 September. This meant that the activities at that meeting were not covered by the requisite undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16. There could be no breach of that undertaking so the Panel ruled no breach of Clause 29 and consequently no breach of Clauses 9.1 and 2.

The Panel accepted the companies' submission that the material used at the ERS meeting reiterated topics that had already been considered by the PMCPA and ruled upon in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel decided that these materials were covered by that ruling and thus decided not to make a separate ruling of breaches of Clauses 3.2 and 7.2 in that regard.

The Panel was concerned that given its rulings in Cases AUTH/2840/4/16 and AUTH/2847/5/16 it appeared that the companies had failed in some representative briefing materials to make Ultibro Breezhaler's licensed indication clear. It did not consider that this necessarily meant that the companies had failed to make it clear to staff what constituted off label use of the product as alleged in Cases AUTH/2928/1/17 and AUTH/2929/1/17. Although it was likely that staff might not be clear, the Panel did not consider that the complainant had shown on the balance of probabilities that the companies had failed to adequately train personnel to recognise that the use of FDC-indacaterol/glycopyrronium to reduce exacerbations in COPD was off label. Further there was no evidence that there would be numerous off label use case reports and if so that these had not been collated for pharmacovigilance maintenance obligations. The Panel therefore ruled no breach of Clause 16.2 and consequently no breach of Clauses 9.1 and 2.

With regard to the scientific service, the Panel noted the companies' submission that they were fully committed to protecting and enhancing patient safety and operated extensive, robust scientific services and pharmacovigilance systems. The Panel did not consider that the companies' failures in Cases AUTH/2840/4/16 and AUTH/2847/5/16 necessarily meant that the relevant staff were not fully conversant with pharmacovigilance requirements relevant to their work nor had the complainant provided evidence in that regard. The Panel therefore ruled no breach of Clauses 25.1 and 15.6 of the Code. The Panel consequently ruled no breach of Clause 9.1 in that regard.

With regard to the materials used at the British Thoracic Society Winter meeting in December 2016, the Panel noted that the companies had not been able to identify the material from the complaint. The companies submitted that the material provided by the complainant had not been used at that meeting and it was likely to be a journal advertisement from early 2016. The companies submitted that the material certainly preceded the date the undertakings were provided in Cases AUTH/2840/4/16 and AUTH/2847/5/16. The Panel noted, however, that the title of the piece 'Ultibro Breezhaler. An evidence-based solution for patients with or without a history of exacerbations' was the same as the current material provided by Pfizer and Novartis (updated sales aid ref UK/ULT/16-0543). The Panel noted Pfizer and Novartis' submission that the licensed indication for Ultibro Breezhaler, as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD, did not stipulate or preclude its use in any subgroup of symptomatic COPD patients including the presence or absence of a history of exacerbations, previous therapy, or success of previous therapy and that it was established in Case AUTH/2840/5/16 and AUTH/2847/5/16, use of Ultibro Breezhaler in adults with COPD who required maintenance bronchodilator therapy to relieve symptoms, irrespective of a history of exacerbations, was entirely within the licensed indication.

The Panel noted that what was actually stated in the Panel ruling in Cases AUTH/2840/4/16 and AUTH/2847/5/16 was that Section 5.1 of the SPC referred to Ultibro's positive impact on exacerbations and the Panel accepted that patients whose symptoms were well controlled might be less likely to experience an exacerbation of their condition than patients with poorly controlled symptoms and in that regard the Panel considered that reference to exacerbation might be included in the promotion of COPD maintenance therapy but there was a difference between promoting a medicine for a licensed indication and promoting the benefits of treating a condition.

The Panel noted the difference of opinion between the complainant and the companies and considered that the complainant had not shown, on the balance of probabilities, that the companies had used the Ultibro advertisement he/she provided at the British Thoracic Society (BTS) meeting in December 2016 and had therefore promoted Ultibro Breezhaler for an unlicensed indication at that meeting as alleged. The Panel therefore ruled no breach of Clauses 3.2 and 7.2 of the Code. The Panel also considered that in these circumstances there could be no breach of the undertaking given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and thus ruled no breach of Clause 29. Consequently there was no breach of Clauses 9.1 and 2.

With regard to the allegation that there was a suggestion that staff on the stand were specifically briefed to discuss Ultibro in the context of the GOLD 2017 Report, the Panel noted the companies' submission that the comments on the derivation of GOLD's recently revised recommendations and what the GOLD committee deemed appropriate management strategies for COPD patients, including the evidence they chose to review or not fell outside the scope of the Code. The companies did, however, agree with the Panel's view that any Novartis – Pfizer materials that related to the GOLD 2017 Report might well fall under the remit of the Code. The Panel examined the materials available on the stand. These included Wedzicha *et al* 2016 (FLAME) and various promotional material some of which referred to the GOLD Guidelines including that 'the goal of treatment was to manage symptoms and reduce the risk of exacerbations'.

The Panel noted that Pfizer and Novartis had briefed staff on 18 November 2016 regarding the GOLD 2017 Report. The Panel noted that the companies briefed its staff regarding an important update on materials following the PMCPA ruling on 16 September 2016. The briefing stated 'You must ensure that when you are talking about exacerbation data for, *inter alia*, Ultibro Breezhaler your customers are clear that the reason to prescribe Ultibro Breezhaler is as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It is acceptable to present data about exacerbations as long as the customer is not left with the impression that Ultibro is treating exacerbations or that the primary reason to prescribe is to reduce exacerbations.

The Panel queried why this had not been re-iterated to staff at BTS considering Ultibro was to be promoted and the briefing regarding the GOLD 2017 Report which had been issued recently (18 November 2016). The briefing document (ref UK/ULT/160673) was headed 'To be used only by authorised Pfizer representatives to respond to external inquiries'. It was dated 18 November 2016 and was sent to the Pfizer Respiratory field team, ADs, RCDs, CECs, LAMs. The briefing summarised key points and listed the main considerations with regard to Ultibro Breezhaler. This included that key definitions for patient classifications would be based only on symptoms and exacerbations and that dual bronchodilators such as Ultibro Breezhaler were recommended as first line treatment regardless of their exacerbation risk and prior to the use of ICS marking a significant shift away from ICS containing combination therapies. The instructions also stated that the FLAME study was included as providing evidence for the use of dual bronchodilation; stating that a LAMA/LABA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients. It was important that Pfizer confidently communicated to clinicians the reference behind this statement in order to position Ultibro Breezhaler as the new standard of care for patients with COPD with or without a history of exacerbations.

The briefing material concluded by stating that as could be seen from the significant changes to the GOLD Guidelines which directly impacted Ultibro, treatment decisions were now much more focused on the symptom burden for the patient and LAMA/LABAs had been given a far more prominent role in the management of COPD. This represented a valuable opportunity for the company to provide prescribers with a simple algorithm to follow which would ensure that patients received the right therapy to manage their COPD and increase their chances of living a healthy, active life.

The briefing material referred to Ultibro as 'the evidence based choice of LAMA/LABA for breathless patients regardless of their exacerbation history' and as 'the new standard of care'. In addition, the Panel queried whether the briefing material was sufficiently clear about the need to ensure that any discussion about the reduction in exacerbations should be a benefit of maintenance therapy and not a reason to prescribe *per se*. The Panel considered, on balance, that the briefing material was not sufficiently clear in this regard and thus ruled a breach of Clause 15.9.

The Panel did not consider, however, that the complainant had proved, on the balance of probabilities, that based on the exhibitor activities for Ultibro Breezhaler at the national scientific concerence in December that those on the exhibition stand were specifically briefed to discuss the medicine within the context of the newly issued recommendations within the revised GOLD Report as alleged. The Panel ruled no breach of Clause 15.9 in that regard.

A slide deck for payors (ref UK/ULTSBR/16-0068(1) 'Supporting the management of COPD' consisted of 68 slides including the burden of COPD on the health system, disease management, the benefits of Ultibro Breezhaler and the future of COPD care. The deck referred to the GOLD guidelines that ICS + LABA was recommended for use only in patients in groups C and D (slide 25). This document included claims that Ultibro Breezhaler was an appropriate steroid free option for the patient for whom LABA/ICS was considered (eg slide 31) which also included the Ultibro indication making it clear the primary reason for prescribing Ultibro and therefore no breach of Clauses 3.2 and 7.2 was ruled. The FLAME study (Wedzicha *et al* 2016) results were given on slide 32 including a comparison of exacerbation rates of Ultibro and Seretide as well as FEV1 and rescue medication use. The Panel considered the FLAME study results were set within the context of the licensed indication and thus it ruled no breach of Clauses 3.2 and 7.2 of the Code.

Material (ref UK/ULTSBR/16-0286) described as 'FLAME Business Card – eprint URL link' promoting the results of FLAME (Wedzicha *et al* 2016) referred to the exacerbation outcomes and their impact on patients at risk of future exacerbations without setting these in the context of the Ultibro licensed indication. A breach of Clause 3.2 was ruled. In addition, this material implied that the exacerbation reduction was a primary reason to prescribe Ultibro Breezhaler which was misleading. A breach of Clause 7.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. Pfizer and Novartis had failed to comply with their undertakings given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 and a breach of Clause 29 was ruled. The Panel noted the importance of undertakings and considered that failure to comply with the undertakings and assurance previously given in Cases AUTH/2840/4/16 and AUTH/2847/5/16 had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2.

The Panel did not accept that there was necessarily an issue if the recommendations in the GOLD 2017 Report were based on best evidence in published literature rather than labelling directives from government regulators. Companies had to ensure that they did not promote a product in a way that was inconsistent with the particulars listed in the SPC. Ultibro was indicated as maintenance therapy to relieve symptoms in COPD.

The Panel noted that the GOLD Report recommended starting therapy with a LABA/LAMA combination because: 'In studies with patient reported outcomes as the primary endpoint LABA/LAMA combination showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs'. 'A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients' and 'Group D patients were at higher risk of developing pneumonia when receiving treatment with ICS'. The Panel noted the complainant's concerns that the GOLD Report did not refer to the PRAC recommendation stating a positive risk – benefit balance for FDC-ICS/LABAs in COPD (that the magnitude of benefit in terms of clinically relevant exacerbation reduction observed was as much as ten-fold greater compared to the slightly increased risk in terms of pneumonia).

In the Panel's view, the GOLD Report implied that Ultibro Breezhaler could be prescribed to reduce exacerbations rather than the reduction of exacerbations being a benefit of using the medicine as maintenance therapy.

The Panel noted that four spotlight webinars were conducted in which health professionals were invited to attend a global broadcast about the updated GOLD Report. Representatives were required to show an introductory slide with all obligatory information including Ultibro's licensed indication for an audience of UK health professionals. The Panel noted its comments above regarding the GOLD briefing and the webinars and considered that whilst the GOLD briefing was not sufficiently clear, the 'upfront' slide required to be shown to UK health professionals set out the indication and therefore the webinars were clear about Ultibro Breezhaler's licensed indication and in that regard were not in breach of Clause 3.2.

Complaint received **4 January 2017**

Case completed **6 July 2017**